

## CLAIMS

We claim:

1. A therapeutic agent carrier, comprising:
  - (a) a reversible gelling copolymer, having  
5 a linear random copolymer of:
    - (i) an N-alkyl substituted [meth-  
lacrylamide derivative; and
    - (ii) a hydrophilic comonomer, wherein an  
amount of said hydrophilic comonomer in the linear random  
10 copolymer is less than about 10 mole% wherein gelation  
occurs with substantially no syneresis,  
said linear random copolymer in the form of a plurality of  
linear chains having a plurality of molecular weights  
greater than or equal to a minimum gelling molecular weight  
15 cutoff, and excluding a substantial amount of copolymer  
chains or polymer chains having molecular weights less than  
the minimum gelling molecular weight cutoff;
    - (b) an aqueous solvent mixed with said  
reversible gelling copolymer as a reversible gelling solution;  
20 and
    - (c) a therapeutic agent mixed with said  
reversible gelling solution as said therapeutic agent  
carrier.
- 25 2. The therapeutic agent carrier as recited in claim  
1, wherein said amount is from about 1.6 mole% to about 2  
mole%.
- 30 3. The therapeutic agent carrier as recited in claim  
1, wherein said N-alkyl substituted [meth-]acrylamide is

selected from the group consisting of N-isopropyl[meth-  
]acrylamide, N,N-diethyl[meth-]acrylamide, N-[meth-  
]acryloylpyrrolidine, N-ethyl[meth-]acrylamide, and  
combinations thereof.

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4. The therapeutic agent carrier as recited in claim  
1, wherein said hydrophilic comonomer is hydrophilic [meth-  
]acryl- compound.

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5. The therapeutic agent carrier as recited in claim  
4, wherein said hydrophilic [meth-]acryl- compound is  
selected from the group consisting of carboxylic acid,  
[meth-]acrylamide, hydrophilic [meth-]acrylic acid ester,  
hydrophilic [meth-]acrylamide derivatives and combinations  
15 thereof.

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6. The therapeutic agent carrier as recited in claim  
5, wherein said carboxylic acid is selected from the group  
consisting of acrylic acid, methacrylic acid and  
20 combinations thereof.

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7 The therapeutic agent carrier as recited in claim  
6, wherein said hydrophilic [meth-]acrylamide derivatives  
are selected from the group consisting of N,N-diethyl[meth-  
]acrylamide, 2-[N,N-dimethylamino]ethyl[meth-]acrylamide, 2-  
25 [N,N-diethylamino]ethyl[meth-]acrylamide, or combinations  
thereof.

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8. The therapeutic agent carrier as recited in claim  
5, wherein said hydrophilic [meth-]acrylic ester is selected  
from the group consisting of 2-[N,N-diethylamino]ethyl[meth-  
]acrylate, 2-[N,N-diethylamino]ethyl[meth-]acrylamide, or combinations  
30 thereof.

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]acrylate, 2-[N,N-dimethylamino]ethyl[meth-]acrylate, and combinations thereof.

9. The therapeutic agent carrier as recited in claim  
5 1, wherein said aqueous solvent is selected from the group consisting of water, and aqueous salt solution.

10. The therapeutic agent carrier as recited in claim  
9, wherein said salt solution is a phosphate buffered  
10 saline.

11. The therapeutic agent carrier as recited in claim  
10, wherein an amount of said solvent is from about 70 wt%  
to about 99 wt%.

12. The therapeutic agent carrier as recited in claim  
1, wherein said therapeutic agent is selected from the group  
consisting of anti-cancer agents, hormones, antibiotics,  
narcotic antagonists, analgesics, anti-inflammatory agents,  
20 anti-depressant, anti-epileptic, anti-malarial agents,  
immunoactivators, growth factors, gene therapy agents,  
oligonucleotides, therapeutic peptides and proteins, chemo-  
embolic material and combinations thereof.

25 13. A method of making a therapeutic agent carrier,  
comprising the steps of:

(a) mixing an N-alkyl substituted [meth-  
]acrylamide derivative with a hydrophilic comonomer in a  
reaction solvent with an initiator forming a reaction  
30 mixture, wherein an amount of said hydrophilic comonomer in  
the linear random copolymer is less than about 10 mole%

wherein gelation occurs with substantially no synerisis;

(b) copolymerizing the reaction mixture and forming a first linear random copolymer having a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum gelling molecular weight cutoff, and excluding a substantial amount of copolymer chains or polymer chains having molecular weights less than the minimum gelling molecular weight cutoff;

(c) isolating and purifying the copolymerized first linear random copolymer and obtaining a second linear random copolymer

(d) mixing the thermally reversible copolymer with an aqueous solvent and making a reversible gelling solution; and

(e) adding a therapeutic agent and obtaining said therapeutic agent carrier.

14. The method as recited in claim 13 wherein said initiator is a free radical initiator.

15. The method as recited in claim 13, wherein said amount is from about 1.6 mole% to about 2 mole%.

16. The method as recited in claim 13, wherein said N-alkyl substituted [meth-]acrylamide is selected from the group consisting of N-isopropyl[meth-]acrylamide, N,N-diethyl[meth-]acrylamide, N-[meth-]acryloylpyrrolidine, N-ethyl[meth-]acrylamide, and combinations thereof.

17. The method as recited in claim 13, wherein said hydrophilic comonomer is hydrophilic [meth-]acryl- compound.

18. The method as recited in claim 17, wherein said hydrophilic [meth-]acryl- compound is selected from the group consisting of carboxylic acid, [meth-]acrylamide,  
5 hydrophilic [meth-]acrylic acid ester, hydrophilic [meth-]acrylamide derivatives and combinations thereof.

19. The method as recited in claim 18, wherein said carboxylic acid is selected from the group consisting of  
10 acrylic acid, methacrylic acid and combinations thereof.

20. The method as recited in claim 18, wherein said hydrophilic [meth-]acrylamide derivatives are selected from the group consisting of N,N-diethyl[meth-]acrylamide, 2-  
15 [N,N-dimethylamino]ethyl[meth-]acrylamide, 2-[N,N-diethylamino]ethyl[meth-]acrylamide, or combinations thereof.

21. The method as recited in claim 18, wherein said  
20 hydrophilic [meth-]acrylic ester is selected from the group consisting of 2-[N,N-diethylamino]ethyl[meth-]acrylate, 2-[N,N-dimethylamino]ethyl[meth-]acrylate, and combinations thereof.

22. The method as recited in claim 13, wherein said  
25 reaction solvent is selected from the group consisting of aqueous solvent, hydrocarbon solvent, and combinations thereof.

23. The method as recited in claim 22, wherein said  
30 aqueous solvent is selected from the group consisting of

water, aqueous salt solution and combinations thereof.

24. The method as recited in claim 22, wherein said hydrocarbon solvent is selected from the group consisting of  
5 oxygenated hydrocarbon, chlorinated hydrocarbon, aromatic hydrocarbon, and combinations thereof.

25. The method as recited in claim 24, wherein said oxygenated hydrocarbon is dioxane.

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26. The method as recited in claim 24, wherein said chlorinated hydrocarbon is chloroform.

15 27. The method as recited in claim 24, wherein said aromatic hydrocarbon is benzene.

28. The method as recited in claim 13, wherein said aqueous solvent is selected from the group consisting of  
20 water, and aqueous salt solution.

29. The method as recited in claim 28, wherein said salt solution is a phosphate buffered saline.

25 30. The method as recited in claim 13, wherein said therapeutic agent carrier is selected from the group consisting of is selected from the group consisting of anti-cancer agents, hormones, antibiotics, narcotic antagonists, analgesics, anti-inflammatory agents, anti-depressant, anti-  
30 epileptic, anti-malarial agents, immunoactivators, growth factors, gene therapy agents, oligonucleotides, therapeutic

peptides and proteins, chemo-embolic material and combinations thereof.

31. A biodegradable thermally reversible graft  
5 copolymer, comprising:  
    (a) a biodegradable polymer; grafted with  
    (b) a side chain selected from the group  
consisting of homo-oligomers of [meth-]acrylamide  
derivatives, co-oligomers of [meth-]acrylamide derivatives,  
10 homo-oligomers of [meth-]acrylamide derivatives  
copolymerized with hydrophilic comonomers, co-oligomers of  
[meth-]acrylamide derivatives copolymerized with hydrophilic  
comonomers.

15 32. The copolymer as recited in claim 31, wherein  
said biodegradable copolymer is selected from the group  
consisting of polyaminoacids, poly(phosphasenes),  
poly(caprolactone), polypeptides, polysaccharides and  
combinations thereof.

20 33. The copolymer as recited in claim 31, wherein  
said oligo [meth-]acrylamide derivative is an N-alkyl  
substituted [meth-] acrylamide derivative.

25 34. The copolymer as recited in claim 31, wherein  
said oligo [meth-]acrylamide derivative side chain is  
randomly copolymerized with a hydrophilic comonomer as a  
linear random oligomer, said linear random oligomer having  
molecular weight less than a minimum gelling molecular weight  
30 cutoff.

35. A reversible gelling copolymer solution, comprising the copolymer as recited in claim 31, mixed with an aqueous solvent.

5           36. A therapeutic agent carrier, comprising:  
the copolymer solution as recited in claim 35,  
mixed with a therapeutic agent.

37. A method of making a biodegradable thermally  
10 reversible copolymer, comprising the steps of:

(a) polymerizing a plurality of side chains selected from the group consisting of homo-oligomers of [meth-]acrylamide derivatives, co-oligomers of [meth-]acrylamide derivatives, homo-oligomers of [meth-]acrylamide  
15 derivatives copolymerized with hydrophilic comonomers, co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers, said side chain having a first active group; and

(b) coupling the side chains to a biodegradable  
20 polymer having a plurality of second active groups wherein said first active group connects to one of the plurality of the second active groups.

38. The method as recited in claim 37, wherein said  
25 biodegradable polymer is selected from the group consisting of polyaminoacid, poly(phosphazenes), poly(caprolactone), polypeptides, polysaccharides and combinations thereof.

39. The method as recited in claim 37, wherein said  
30 polymerizing is a free radical copolymerization wherein the first active group is an amino which originates from an amino-terminated chain transfer agent.



40. The method as recited in claim 39, wherein said amino-terminated chain transfer agent is 2-aminoethanethiol hydrochloride.

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41. The method as recited in claim 37, wherein said coupling is with an activation reagent.

42. The method as recited in claim 39, wherein said  
10 activation reagent is dicyclohexyl carbodiimide.

43. The method as recited in claim 37, wherein said oligo [meth-]acrylamide derivative is an N-alkyl substituted [meth-] acrylamide derivative.

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44. The method as recited in claim 37, wherein said oligo [meth-]acrylamide derivative side chain is randomly copolymerized with a hydrophilic comonomer as a linear random oligomer, said linear random oligomer having  
20 molecular weight less than a minimum gelling molecular weight cutoff.

45. The method as recited in claim 37, further comprising the step of:

25 mixing the biodegradable copolymer with an aqueous solvent.

46. The method as recited in claim 45, further comprising the step of:

30 adding a therapeutic agent and obtaining a therapeutic agent carrier.